Nitrile and Non-nitrile Pyridine Products from the Reaction of 2-Cyano-3-(*x*-nitrophenyl)prop-2-enamides with Methyl 3-Oxobutanoate

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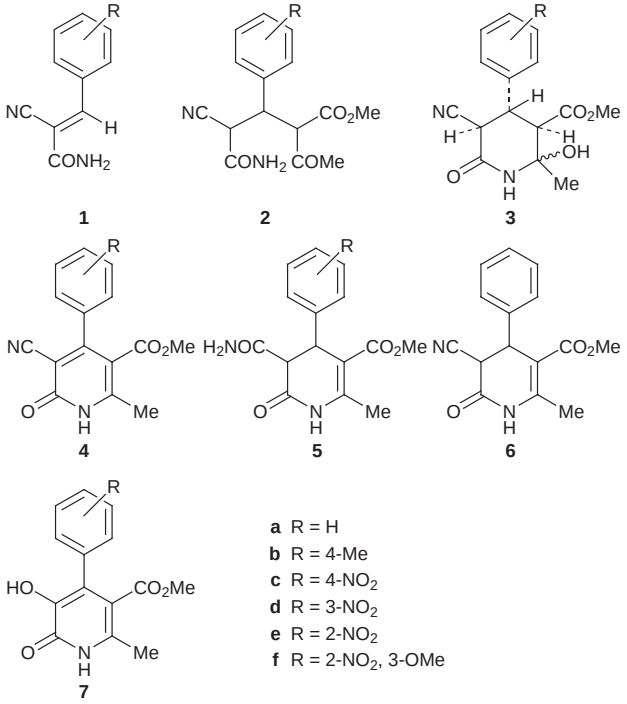
The reaction of 2-cyano-3-(*x*-nitrophenyl)prop-2-enamides with methyl 3-oxobutanoate affords methyl 4-aryl-3-cyano-6-methyl-2-oxo-1,2-dihydropyridine-5-carboxylates, methyl 4-aryl-5-cyano-2-hydroxy-2-methyl-6-oxopiperidine-3-carboxylates, methyl 4-aryl-3-carbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylates (the molecular structure of one of which has been confirmed by X-ray diffraction) and methyl 4-aryl-3-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-5-carboxylates.

In recent years, pyridin-2-one derivatives have shown significant activity as HIV-1 specific reverse transcriptase inhibitors.[1,2] In a continuing study of the synthesis of polysubstituted pyridin-2-ones,[3] we find that the reaction of 2-cyanocinnamamide **1a** with methyl 3-oxobutanoate affords the piperidin-2-one derivative **3a**, together with the dihydropyridin-2-one **4a**. The *p*-tolyl amide derivative **1b** behaves like its phenyl analogue **1a**, affording the piperidin-2-one **3b** and dihydropyridin-2-one **4b** products.

Significantly different results are obtained when nitrophenyl derivatives **1** ($R = NO_2$) are used. In the case of the *m*-nitro derivative **1d**, the piperidin-2-one product **3d** is accompanied by the 3-carbamoyl-1,2,3,4-tetrahydropyridin-2-one **5d**, while the *p*-nitro derivative **1c** affords the dihydropyridin-2-one **4c** accompanied by the tetrahydropyridin-2-one **5c**.



The formulation **5c** is confirmed by X-ray crystallography (Fig. 1), which shows that the two C–H protons in the tetrahydropyridin-2-one ring are *trans*, with a dihedral angle of 71.6° (these protons display no discernible coupling in the ^{1}H NMR spectrum). It is interesting to compare the structure shown in Fig. 1 with the recently published X-ray of the related 3-cyano compound **6**.[6] In the latter, which was obtained as a by-product *via* a quite different synthetic route, the *cis*-orientation of the two ring protons (dihedral angle 46.3°; observed coupling constant $J = 9$ Hz) is strikingly different.

When the *o*-nitrophenyl amide derivative **1e** reacts with methyl 3-oxobutanoate, two non-nitrile pyridine products are obtained, together with the piperidin-2-one **3e** and the dihydropyridin-2-one **4e**; the non-nitriles are the 3-carbamoyl tetrahydropyridin-2-one **5e** and another product identified as the 3-hydroxy derivative **7e**. A second *o*-nitrophenyl derivative **1f** also affords a 3-carbamoyl tetrahydropyridin-2-one **5f** and a 3-hydroxy derivative **7f**, together with the dihydropyridin-2-one **4f**.

It is assumed that the open-chain compounds **2** are the initial intermediates in these reactions. Consideration of the results makes it clear that under the mild basic conditions employed, cyclisation of the intermediates **2** ($R = NO_2$) takes place not only as expected through reaction of the carbamoyl group to form **3** and **4** ($R = NO_2$), but also through the nitrile group to form **5** ($R = NO_2$). It is also clear that when an *o*-nitrophenyl substituent is present, the nitrile group in the pyridine product may be replaced by OH.

It seems probable that cyclisation of the intermediates **2** through a nitrile group may involve formation of an unisolated aminopyran derivative which then undergoes Dimroth rearrangement to a pyridin-2-one.[7,13] The mechan-

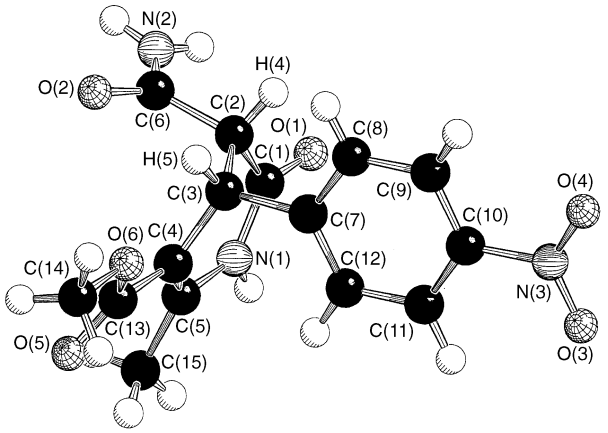


Fig. 1 Molecular structure of methyl 3-carbamoyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate **5c**

* To receive any correspondence.

Table 7 Crystal data and structure refinement for methyl 3-carbamoyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate **5c**

Empirical formula	$C_{15}H_{15}N_3O_6$
M	333.30
T/K	293(2)
λ/Å	0.71073
Crystal system, space group	Triclinic, $P\bar{1}$
Unit cell dimensions	
a/Å	6.4505(9)
b/Å	7.7918(10)
c/Å	16.2999(19)
α/°	98.627(9)
β/°	100.270(10)
γ/°	102.474(10)
V/Å^3	771.79(17)
D_c/g cm^{-3}	2, 1.434
μ/mm^{-1}	0.113
F(000)	348
Crystal size/mm	$0.3 \times 0.4 \times 0.5$
θ range/°	1.29–24.97
Limiting indices, hkl	0 to 7, −8 to 8, −17 to 17
Reflections collected/unique	2917/2664
R_{int}	0.0175
Completeness to $\theta = 24.97(\%)$	
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2664/0/277
Goodness-of-fit on F^2	1.042
Final R indices $[I > 2\sigma(I)]$	$R1 = 0.0447$, $wR2 = 0.1014$
R indices (all data)	$R1 = 0.0814$, $wR2 = 0.1164$
Largest diff. peak and hole/e Å^{-3}	0.254 and −0.166

ism through which the compounds **7** are formed, with a hydroxy group present as 3-substituent rather than a nitrile, presents a more difficult problem. The literature records a couple of instances of direct replacement of C≡N by OH,[14,15] but no mechanistic route was postulated. It is suggested that a 3-cyanotetrahydropridin-2-one intermediate may, because of the presence of the adjacent nitro group, form an equilibrium resulting in activation of the 3-position and subsequent replacement of C≡N by O.

Crystal Structure Determination of Methyl 3-*Carbamoyl*-6-*methyl*-4-(4-*nitrophenyl*)-2-*oxo*-1,2,3,4-*tetrahydropyridine*-5-*carboxylate* **5c**.—Data were collected on an Enraf-Nonius CAD-4 diffractometer (Mo-Kα radiation, graphite monochromator, ω-2θ scans) at 20 °C. The data and experimental parameters obtained from the colourless prismatic crystals are given in Table 7. The final cell parameters were determined using the Celdim routine. It was not found necessary to apply decay or absorption corrections to the data. The data were reduced to give the number of unique reflections and those with $|F| > 4\sigma|F|$ were used in structure solution and refinement.

The structure was solved by automatic direct methods using SHELXS-86.[20] The structure was refined by full-matrix least-squares analysis on F^2 with SHELXL.[21] The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were located from subsequent difference Fourier maps and refined with individual temperature factors to a final R value $[I > 2\sigma(I)]$ of 4.5%.

Techniques used: IR, ^{1}H NMR, ^{13}C NMR, CH COSY and NOE, X-ray crystallography, elemental analysis

References: 21

Fig. 2: A packing diagram for compound **5c**

Tables 1, 3, 5: Microanalytical data for compounds **4**, **3**, **5**

Tables 2, 4, 6: Spectral data for **4**, **3**, **5**

Table 8: Atomic coordinates and equivalent isotropic displacement parameters for **5c**

Table 9: Bond lengths and angles for **5c**

Table 10: Anisotropic displacement parameters for **5c**

Table 11: Hydrogen coordinates and isotropic displacement parameters for **5c**

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